Remarks

Introduction

Claims 37, 58, 66 and 67 have been amended, no claims have been added. Thus, with the entry of this amendment, claims 37- 43, 47, 54-58, 66 and 67 will be active in this case.

In the Office Action dated March 26, 2003, the Examiner has withdrawn the previous grounds of rejection, except for the outstanding obviousness rejection of claims 37 and 58. However, the Examiner has entered new grounds of rejection, which are discussed below. Reconsideration and withdrawal of any objections and rejections in view of the foregoing amendments and remarks set forth below are respectfully requested.

Prior Art Rejections

In paragraph 9, the Examiner has maintained the rejection of claims 37, 58, 66 and 67 under 35 U.S.C. § 103 for obviousness over Seemann (EP 501,215) and Mattes (*J. of Natl. Cancer Inst.*, 79(4): 855 (1987)). Specifically, the Examiner states that Mattes teaches glycosylation resulting in a moiety that comprises galactose and that the claims recite that the carbohydrate comprises galactose. The rejection is applied to new claims 66 and 67 because these claims are drawn to conjugates or fusion proteins where the enzyme is ß-glucoronidase and Seemann is said to teach a conjugate and fusion glycoproteins comprising ß-glucoronidase. The Examiner admits that Seemann does not teach or suggest glycosylation of the disclosed agents, as instantly claimed. Applicants respectfully traverse the rejection.

The Examiner cites Mattes for teaching agents with carbohydrate complements. However, Mattes is directed to conjugating antibodies, specifically with aminophenyl-lactose or cyano-methyl-galactose. No combination of the teachings of Seeman with Mattes results in a fusion glycoprotein or conjugate thereof comprising at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose.

Although Mattes mentions that antibodies may be galactosylated to increase clearance from the blood, one skilled in the art might question whether rapid clearing of the construct would be desireable in view of the tumor targeting function of the antibody. Thus, contrary to the Examiner's conclusion, it is unlikely that one of skill in the art would have been motivated to apply Mattes's suggestion of rapid clearance to arrive at the present invention.

Moreover, the combination of Seemann and Mattes does not provide a reasonable expectation that the claimed glycoprotein conjugates would be successful. Mattes does not teach a fusion construct having **enzyme activity**. Rather, Mattes teaches an antibody that is linked to a radioisotope, a toxin or a drug. In fact, Mattes teaches at column 6, line 65 to column 7, line 5 that the exposure of lectin-binding glycoside residues of an antibody might be changed in an unpredictable manner by enzyme activity. Such a statement suggests that the glycosylation might negatively affect enzymatic activity. Arguably, this teaching not only fails to provide the requisite expectation of success in having the enzymatic activity of the claimed invention, it guides the skilled artisan **away from** the claimed invention. Accordingly, reconsideration and withdrawal of the obvious ness rejection over Seeman and Mattes are respectfully requested.

In paragraph 10 of the Office Action, the Examiner has rejected claims 37, 38, 40, 41, 43, 47, 54, 58, 66, and 67 as obvious over Canadian Patent No. 2,062,047 to Seemann (Seemann '047) in view of U.S. Patent No. 4,859,449 to Mattes (Mattes '449) or Winkelhake, *Biological Chemistry,* 251(4): 1074-1080, 1976 (Winkelhake). Applicants respectfully traverse this rejection.

Seemann '047 allegedly teaches glycoprotein fusion proteins and conjugates that comprise antibody binding fragments of BW431/26 monoclonal antibody linked to a ß-glucoronidase, and teaches such fusion proteins and conjugates in methods for targeted prodrug activation at tumors. The Examiner admits that Seemann '047 fails to teach glycoprotein fusion proteins or conjugates that comprise an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose. The Examiner maintains, however, that it is known to modify antibodies by adding sugar, as taught in Mattes. Winkelhake is cited for teaching A

method of enzymatic degradation and the desireability of doing so to enhance antibody clearance. Applicants respectfully traverse this rejection.

Applicants arguments set forth above in connection with the rejection over Mattes and Seemann are applicable to this rejection as well. However, applicants further argue that Winkelhake is a good reference for demonstrating the complexity of enzymatic degradation of carbohydrates. That is, Winkelhake discloses that with regard to rabbit antibodies, the clearance of antibodies decreases and increases depending upon a stepwise cleavage of the sugar complexes. One of skill in the art reading this would expect to observe many intermediary effects by having the different sugars only partially removed. The situation would become even more complex where the antibody carries an enzyme which is capable of interfering with its own glycosylation, i.e, the enzyme is active on its own sugar residues. Arguably, such complexities support applicants previous contention that the cited art does not provide a reasonable expectation of success at arriving at the invention. Applicants respectfully request the Examiner to withdraw this rejection.

In paragraph 11, the Examiner also has rejected claims 37 and 56 over Seemann '047, in view of U.S. Patent No. 4,859,449 to Mattes or Winkelhake, in further view of Bosslet (Br. J. Cancer 65: 234-238 (1992)) and Jahde (Cancer Res. 52:6209 (1992) (Abstract)). Applicants respectfully traverse this rejection.

The Examiner cites Bosslet for allegedly teaching that ß-glucoronidase increases in activity with a pH lower than the physiological pH. Jahde is cited for teaching methods of lowering intracellular pH. The Examiner concludes that it would have been *prima facie* obvious to one of skill in the art at the time of the invention to have included an agent for lowering intracellular pH of tumor cells.

Applicants argue that Bosslet and Jahde do not cure the deficiencies in the primary references, as discussed above. With regard to the invention of claim 56, applicants argue that Bosslet's teachings do not guide the skilled artisan toward the invention. Specifically, Bosslet disclosed an increased activity of a specific enzyme at reduced pH values. However, maximum activity occurred at a pH value of 4.5. It would have been unclear from the disclosed data

whether the results of this experiment would have been applicable to living cells. Intracellular pH values are expected to occur at about 7. However, specialized organelles, such as lysosomes are reported to provide for pH conditions around 4.0. The fact that methods of lowering intracellular pH were known , as evidenced by Jahde, is simply irrelevant to the claimed invention as a whole. There must be a motivation to combine teachings and an expectation of success and such motivation and expectation must come from the cited references, not hindsight based on knowledge of the invention. Applicants respectfully request the Examiner to withdraw this rejection.

In paragraph 12, the Examiner also has rejected claims 37, 54, and 55 as obvious over Seemann in view of Winkelhake, in further view of U.S. Patent No. 5,545,405 to Page (Page). In paragraph 13, the Examiner also has rejected claims 37 and 57 over Seemann in view of Mattes or Winkelhake in further view of Bagshawe. Applicants respectfully traverse these rejections.

The Examiner argues that the production of antibodies in CHO cells, as taught by Page, renders the inventions of claims 54 and 55 obvious when Page is combined with the method of Seemann. Applicants respond that Page and the other cited references fail to cure the deficiencies in the primary references, as discussed above. The fact that CHO cells were known for making antibodies is irrelevant to the invention as a whole in the absence of the requisite motivation and expectation of success. Accordingly, reconsideration and withdrawal of the rejections under § 103(a) are respectfully requested.

With regard to claim 57, applicants reiterate that Bagshave does not cure the deficiencies in the primary references. Additionally, applicants point out that Bagshave's teachings are not necessarily generally applicable. Rather, Bagshave discloses the use of asialofetain to decrease the clearance of very specific fusion proteins. It doesn't teach the use of galactose in a pharmaceutically acceptable carrier. Applicants believe that, at best, Bagshave's teachings are an invitation to experiment, which is not a proper basis for an obviousness rejection.

Rejections under 35 U.S.C. § 112, first paragraph

In paragraph 14, the Examiner has rejected claims 37-43, 47 and 54-58 under 35 U.S.C. § 112, first paragraph as non-enabled. The Examiner states that the specification fails to describe how to make the claimed monoclonal antibody BW 431/26. In paragraph 15, the examiner has rejected claim 42 under 35 U.S.C. § 112, first paragraph as non-enabled and states that a carbohydrate residue produced by chemical degradation is not enabled since the specification does not teach those chemical processes which will make the exposed carbohydrate. Applicants respectfully traverse these rejections.

With regard to the production of BW 431/26, applicants point out that aside from what the present specification teaches, BW 431/26 is a known antibody that has been disclosed publicly, in detail. That is, this antibody and the production thereof is described in detail in Seemann '047 (Canadian Patent No. 2,062,047). Seemann '047 also teaches the assays necessary for testing the described antibody. Although experimentation would be necessary to obtain BW 431/26, such experimentation would not be "undue experimentation;" rather, it would be routine to the skill of the art of the invention. Thus, applicants respectfully request the Examiner to withdraw this rejection.

With regard to claim 42, applicants assert that methods of chemically degrading carbohydrates are well known in the field of biochemistry. Accordingly, reconsideration and withdrawal of the rejection under § 112, first paragraph, are respectfully requested.

Claim Objections

The Examiner has objected to claim 47 for reciting other tumor specific antigen besides CEA. However, notwithstanding the fact that BW 431/26 binds CEA, Applicants respectfully submit that the claims recite a portion which comprises a monoclonal antibody BW 431/26, and therefore, can have other portions that bind tumor specific antigens recited in claim 47, besides CEA. Accordingly, reconsideration and withdrawal of objection are respectfully requested.

Conclusion

Based on the foregoing, Applicants urge that the claims are in condition for allowance. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, then Examiner Holleran is respectfully invited to contact the undersigned at the local exchange listed.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Director is hereby authorized to charge Deposit Account No. 08-1641 for any such fees; and Applicants hereby petition for any needed extension of time.

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37. **(Three Times Amended)** A pharmaceutical kit comprising:

(a) a first component comprising a bifunctional fusion glycoprotein or conjugate thereof comprising

(i) at least one first portion which is an enzyme selected from the group consisting of penicillin G amidase, penicillin V amidase, β-lactamase, alkaline phosphatase, carboxypeptidase G2, carboxypeptidase A, cytosine deaminase, nitroreductase, diaphorase, arylsulfatase, glycosidase, β-glucosidase, and β-glucuronidase; and

(ii) at least one second portion which comprises a monoclonal antibody BW 431/26 or an antigen binding fragment thereof that binds said first component to a tumor-specific antigen on a tumor cell;

wherein said fusion glycoprotein or conjugate thereof comprises **[at least one carbohydrate complement comprising]** at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose; and

(b) a second component comprising a non-toxic prodrug that is subsequently cleaved into a tumor cytotoxic drug by said enzymatic activity of said first component,

wherein each of said first and said second components is in a pharmaceutically acceptable vehicle.

58. **(Three Times Amended)** A method of treating a tumor in a subject, comprising:

(a) administering to said subject in a first step, a first component comprising a bifunctional fusion glycoprotein or conjugate thereof comprising

(i) at least one first portion which is an enzyme selected from the group consisting of penicillin G amidase, penicillin V amidase, β-lactamase, alkaline phosphatase, carboxypeptidase G2, carboxypeptidase A, cytosine deaminase, nitroreductase, diaphorase, arylsulfatase, glycosidase, β-glucosidase, and β-glucuronidase; and

(ii) at least one second portion which comprises a monoclonal antibody BW 431/26 or an antigen binding fragment thereof that binds said first component to a tumor-specific antigen on a tumor cell;

wherein said fusion glycoprotein or conjugate thereof comprises **[at least one carbohydrate complement comprising]** at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose; and

(b) administering to said subject in a second step, a second component comprising a non-toxic prodrug that is subsequently cleaved into a tumor cytotoxic drug by said enzymatic activity of said first component,

wherein each of said first and said second components is in a pharmaceutically acceptable vehicle.

66. **(Amended)** A pharmaceutical kit comprising:

(a) a first component comprising a bifunctional fusion glycoprotein or conjugate thereof of the formula huTuMab-L-β-Gluc, wherein huTuMab is a human tumor specific monoclonal antibody or an antigen binding fragment thereof, L is said linker molecule, and β-Gluc is a human β-glucuronidase;

wherein said glycoprotein or conjugate thereof comprises **[at least one carbohydrate complement comprising]** at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose; and

(b) a second component comprising a non-toxic prodrug that is subsequently cleaved into a tumor cytotoxic drug by said enzymatic activity of said first component.

67. **(Amended)** A method of treating a tumor in a subject, comprising:

(a) administering to said subject in a first step, a first component comprising a first component comprising a bifunctional fusion glycoprotein or conjugate thereof of the formula huTuMab-L-β-Gluc, wherein huTuMab is a human tumor specific monoclonal antibody or an antigen binding fragment thereof, L is said linker molecule, and β-Gluc is a human β-glucuronidase;

wherein said glycoprotein or conjugate thereof comprises **[at least one carbohydrate complement comprising]** at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose; and

(b) administering to said subject in a second step, a second component comprising a non-toxic prodrug that is subsequently cleaved into a tumor cytotoxic drug by said enzymatic activity of said first component.